UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)(KMW)**

PLAINTIFFS' BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT MICHAEL B. BOTTORFF, PHARM. D.

HOLLIS LAW FIRM
8101 College Blvd, Suite 260
Overland Park, KS 66210
913-385-5400
913-385-5402 fax

On the Brief:
C. Brett Vaughn RN, BSN, JD

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page No.

Cases

Rules

PRELIMINARY STATEMENT

Michael Bottorff, Pharm. D., a pharmacist retained by the Defendants, submitted a report disputing general causation. However, in deposition Dr. Bottorff admitted that NDMA is a probable carcinogen, that he didn't follow the FDA's methodology when converting the equivalent dose of a carcinogenic substance in animals to humans, that he isn't sure that extrapolating from animals to humans is accurate or the right thing to do, that genotoxins are outside of his area of expertise, and that if the WHO recommended against interspecies scaling with NDMA because it is a genotoxin, that he possibly would have changed his methodology. Furthermore, Dr. Bottorff only sought out studies that showed doses of NDMA that didn't cause cancer in animals and did not look for studies that showed equivalent or lower doses of NDMA causing cancer in animals. Dr. Bottorff's methodology was flawed from the start, in that he only sought out information that would support the opinions he was hired to give.

Similar to other defense experts, Dr. Bottorff ignored and did not factor in significant categories of evidence that strongly support the designation of NDMA and NDEA as human carcinogens, including animal studies, dietary studies, occupational studies, and mechanistic studies – all of which were taken into account by Plaintiffs' general causation experts. Dr. Bottorff also admitted that he did not do any research into how genotoxic carcinogens behave, and that his only experience with genotoxic carcinogens was prescribing a medication that was later found to be mutagenic and caused bladder cancer.

The foundation and application of Dr. Bottorff's methodology was unreliable. Therefore, Dr. Bottorff's opinions on general causation should be precluded.

STATEMENT OF FACTS

1. Dr. Bottorff's Lack of Qualifications

Dr. Bottorff is a pharmacist. He is not a cancer researcher, epidemiologist, toxicologist, oncologist, or risk assessor, nor is he holding himself out as an expert in these fields. (9/16/2021 Michael B. Bottorff Dep. Tr. 112:2-3, 117:17-19, 214:4-10, 221:5-223:21, 300:9-22 [hereinafter, "Bottorff Dep."], Ex A). Prior to this litigation the only experience that Dr. Bottorff had with a genotoxin carcinogen was prescribing Actos, a drug that caused bladder cancer, though he never got "into the details of the mechanisms of mutagenicity or carcinogenicity." (Bottorff Dep. 379:4-10; 160:14-161:7). Dr. Bottorff isn't even sure if a substance can be carcinogenic but not genotoxic. (Bottorff Dep. 379:12-18). In spite of his lack of knowledge regarding genotoxins, Dr. Bottorff did not look for or consider any literature on genotoxic chemicals, because he did not believe it to be germane to the focus of his report. (Bottorff Dep. 331:14-23). It appeared that most of Dr. Bottorff's opinions focused on the metabolism of NDMA, however when pushed on this subject in deposition, Dr. Bottorff retreated and testified "And again, ***my focus for this report was to try to find studies that gave doses that did not produce cancer***." (Bottorff Dep. 303:24-304:10 (emphasis added)). Dr. Bottorff did not attempt to seek out or consider studies that were contrary to the opinion he was hired to provide.

2. Dr. Bottorff's Disclaimed Opinions

Dr. Bottorff is not generally disputing the carcinogenicity of NDMA and NDEA in humans, or even if the levels found in valsartan could increase the risk of a person developing cancer. In fact, when specifically asked if it was his opinion that the levels of NDMA in generic valsartan are unable to increase a person's risk of developing cancer, Dr. Bottorff candidly responded, "I don't

think I'd characterize my opinion as being unable. I don't think I used those terms anywhere." (Bottorff Dep. 15:6-15).

3. Dr. Bottorff's Methodology

a. Biased, One-Sided Literature Review

Dr. Bottorff's methodology was severely flawed from the very beginning, in that he only looked for studies that would support his opinion that the levels of NDMA in contaminated valsartan don't cause cancer, as evidenced by him testifying "But again***, I was looking for doses that didn't cause cancer, not doses that did***." (Bottorff Dep. 297:18-20), and "my focus for this report was to try to find studies that gave doses that did not produce cancer." (Bottorff Dep. 304:8-10).

As a result, Dr. Bottorff did not consider mechanistic, dietary, or occupational exposure studies, which clearly demonstrate NDMA increasing the risk of cancer in humans, even at the doses present in valsartan. Failure to consider an entire category of evidence is a fatal methodological flaw.

b. Rat to Human Extrapolations Counter to WHO Recommendation

When asked what his basis was for extrapolating from rats to humans at a one-to-one ratio, Dr. Bottorff admitted "Well, as I've already said, ***we are not sure that extrapolating these animal data to humans is accurate and the right thing to do to begin with***." (Bottorff Dep. 272:3-23 (emphasis added)). Dr. Bottorff then testified that he doesn't know the reason that it takes half as much NDMA per kg to induced tumors in rats compared to mice. (Bottorff Dep. 289:24-290:24). When asked if he looked for literature as to whether mutagenicity could impact interspecies scaling, Dr. Bottorff candidly responded, "I don't even know that that's the question that I was

looking at." (Bottorff Dep. 164:9-13). Then, when confronted with a World Health Organization (WHO) document that was listed on Dr. Bottorff's materials considered, which states:

> **Scaling for variations in the ratios of surface area to body weight between rodent species and humans was not considered appropriate** for the measures of exposure response developed on the basis of experimental data in animals, since it's highly probably that the carcinogenicity of NDMA is mediated primarily through the generation of an active metabolite.

(WHO 2002, Ex. B at p. 23 (emphasis added); Bottorff Dep. 310:23-311:8). Dr. Bottorff confessed, "I don't recall specifically that comment." (Bottorff Dep. 312:15-16). While Dr. Bottorff wasn't sure if the WHO considered interspecies scaling for NDMA exposure to be inappropriate because NDMA is a genotoxin or because of how it's metabolized, he did admit that if it was because NDMA is a genotoxin that he would have possibly changed his methodology. (Bottorff Dep. 313:3-314:15). Dr. Bottorff also admitted that the active metabolite is a genotoxin. (Bottorff Dep. 313:3-5).

c. Dose Conversions Counter to FDA Guidance

Instead of following WHO recommendations, Dr. Bottorff took a few rat studies that he found and believed were "fairly consistent" in the milligrams per kilogram of NDMA that were administered to the rats and didn't cause cancer, and then multiplied by 70 because the average weight of an adult human is 70kg. (Bottorff Dep. 270:9-16). Dr. Bottorff admitted that he did not do any research to make sure that 70 was the appropriate number to multiple by when dealing with a carcinogen. (Bottorff Dep. 264:12-18). Upon being confronted with the FDA's 2018 guidance for industry, Dr. Bottorff admitted that when dealing with a carcinogen that can be extrapolated from animals to humans, the FDA multiplies by 50, not 70. (Bottorff Dep. 280:16-281:2). Dr. Bottorff also conceded that multiplying something by 70 like he did, instead of by 50 like the FDA does, will result in a higher number every time. (Bottorff Dep. 282:10-15). Dr. Bottorff mistakenly

relied on his experience as a pharmacist in multiplying by 70, and did not do any research into carcinogen conversions, which would have revealed that when it's appropriate to convert carcinogenic doses from rodents to humans (it's not with NDMA), you multiple by 50. (Bottorff Dep. 263:22-264:18).

d. Insufficient Knowledge Basis for NDMA Metabolism Opinions

Dr. Bottorff also offers opinions on how valsartan and NDMA is metabolized in humans, yet only identifies the bioavailability of valsartan in his expert report, and never identifies the bioavailability of NDMA. (Expert Report of Michael Bottorff, Pharm. D., p. 21 [hereinafter, "Bottorff Report"], Ex. C). In deposition, Dr. Bottorff testified that unlike valsartan, NDMA must fully saturate the liver before there would be systemic exposure to NDMA, because NDMA is metabolized faster than valsartan. (Bottorff Dep. 186:17-189:24). Dr. Bottorff then conceded that he did not know the rate of metabolism for NDMA or valsartan. (Bottorff Dep. 190:2-9). In addition, Dr. Bottorff conceded that if orally ingested NDMA is observed in the blood, then it means that the dose was high enough to pass the liver, and therefore, organs that receive blood flow would be exposed to NDMA. (Bottorff Dep. 153:19-155:4, 247:21-248:2). Furthermore, Dr. Bottorff admitted that he never bothered to look at studies that demonstrated that NDMA and NDEA levels would increase in the blood after oral ingestion of NDMA and NDEA. For example, at deposition, Dr. Bottorff was shown that the paper by Pegg on the metabolism of NDMA, which Dr. Bottorff cited numerous times in his expert report (Bottorff Report p. 27, 30, 33), says that NDMA and NDEA levels increase in the blood of humans after eating a meal. Dr. Bottorff responded that he would have to look at the studies on that because he did not look at them in

forming his opinions. (Bottorff Dep. 257:12-258:22).[1]

When the defense attempted to rehabilitate Dr. Bottorff by asking him if he determined the first-pass metabolism (bioavailability) of NDMA, Dr. Bottorff testified "For NDMA, that assessment is not as exact a science, except for a couple small rat studies that looked at it, because you don't want it to get into the systemic circulation." (Bottorff Dep. 357:20-360:7). Furthermore, when the defense asked Dr. Bottorff if he was able to determine a liver saturation level for NDMA or NDEA, Dr. Bottorff answered, "Not in the context of what the actual dose would be based on blood levels past the liver because it has such a short half-life that it's really difficult to do." (Bottorff Dep. 362:12-18).

e. Dose Threshold Opinion Relies Solely on Underpowered Studies

Dr. Bottorff also opined that he disagreed with plaintiffs' experts that opined NDMA does not have a dose threshold.[2] (Bottorff Report p. 36; Bottorff Dep. 196:11-20). Dr. Bottorff primarily relied on a study by Peto and a study by Ito for his opinion that NDMA has a dose threshold. (Bottorff Dep. 196:24-197:16). When confronted with the fact that Peto stated in his study that he believed there was a **linear response without a dose threshold for NDMA**, Dr. Bottorff testified "everyone pretty much already believed that it was linear" and "I think there are other experts in this field who might argue that we have more modern data that dispute a low range linearity relationship." (Bottorff Dep. 198:14-203:1). In the Peto study, each dose of NDMA was administered to 120 rats. (Peto, Ex. E). Dr. Bottorff testified that Peto "didn't do enough animals and you don't see enough cancer at those doses to have reliability." (Bottorff Dep. 200:19-21).

[1] Dr. Bottorff had already testified that the average American is only exposed to a few hundred nanograms of NDMA per day in their diet (Bottorff Dep. 250:9-20), and then that some valsartan tablets contained 10s of thousands of nanograms of NDMA (Bottorff Dep. 259:23-260:4).

[2] Like the Plaintiffs' experts, the FDA also considers NDMA and NDEA to have a linear response "with no established threshold mechanism." (2021 FDA Control of Nitrosamine Impurities at p. 24, Ex. D).

The Ito study that Dr. Bottorff relied on was significantly more underpowered than the Peto study, as the lowest doses of NDMA were only administered to 27 rats. (Ito, Ex. F). Finally, when asked if he was aware of the widely understood principle that animal studies may simply be underpowered to pick up the cancer risk at very low levels, Dr. Bottorff responded, "I am aware of any study can be limited by the lack of something showing up at low doses. And that's what we have. That's the data that we have." (Bottorff Dep. 339:10-21). Dr. Bottorff thus relied on underpowered studies for his opinion that NDMA has a dose threshold, and ignored the contrary finding in the seminal study on the topic.

I. THE *DAUBERT* STANDARD

The admissibility of expert testimony is determined pursuant to Federal Rule of Evidence 702. "As a gatekeeper, courts are supposed to ensure that the testimony given to the jury is reliable and will be more informative than confusing." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 800 (2017). The party offering the proposed expert testimony bears the burden of establishing the admissibility of the testimony by a preponderance of the evidence. *Padillas v. Stork-Gamco, Inc.,* 186 F.3d 412, 417-18 (3d Cir. 1999). An "expert's opinions must be based on the methods and procedures of science, rather than on subjective belief or unsupported speculation." *In re Paoli R.R. Yard PCB Litigation*, 35 F.3d 717, 742 (3d Cir. 1994) (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." *Id.* (quoting *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 590 (1993)). Additionally, "[b]oth an expert's methodology and the application of that methodology must be reviewed for reliability." *Zoloft*, 858 F.3d at 791. The "specific way an expert conducts such an analysis must be reliable; '**all of the relevant evidence must be gathered**, and **the assessment or weighing of that evidence must not be arbitrary**, but must itself be **based on**

methods of science.'" *Id.* at 796. These good grounds must support each step of the analysis and, "*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Id.* at 745. Judges within this Circuit also consider how and when the methodology is used outside of litigation. *Paoli*, 35 F.3d at 742 (discussing reliability factors under *Daubert* and Third Circuit case law).

Furthermore, "*Daubert*'s gatekeeping requirement .... make[s] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F.Supp.2d 584, 594 (D.N.J.2002*), aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003). In addition, the following factors are relevant when determining reliability:

> (i) whether the expert's proposed testimony grows naturally and directly out of research the expert has conducted independent of the litigation (*see Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 43 F.3d 1311, 1317 (9th Cir. 1995)); (ii) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion (*see General Elec. Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)); (iii) whether the expert has adequately accounted for alternative explanations (*see Claar v. Burlington, N.R.R.,* 29 F.3d 499 (9th Cir. 1994)).

Magistrini, 180 F. Supp. 2d at 594–95. To this end, the Third Circuit has affirmed the exclusion of expert testimony that "failed to consistently apply the scientific methods … articulate[d], … deviated from or downplayed certain well-established principles of [the] field, and … inconsistently applied methods and standards to the data so as to support [an] a priori opinion." *Zoloft*, 858 F.3d at 792.

II. DR. BOTTORFF'S OPINIONS SHOULD BE PRECLUDED PURSUANT TO DAUBERT

Dr. Bottorff has no relevant experience with carcinogenic substances and wasn't even positive if a substance can be carcinogenic without being genotoxic. (Bottorff Dep. 379:4-18). To make matters worse, Dr. Bottorff didn't even attempt to educate himself on genotoxins. (Bottorff Dep. 331:14-23). This lack of knowledge and experience should result in greater scrutiny of the method actually applied by the expert. *See Elcock*, 233 F.3d at 747 (quoting *Paoli*, 35 F.3d at 742, n.8). Dr. Bottorff also formed his opinions in this case solely for the purposes of litigation. Dr. Bottorff has never researched how a carcinogen is metabolized or the dose needed to cause cancer prior to this litigation. This should factor into the Court's determination of reliability:

> One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying. That an expert testifies for money does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture. But in determining whether proposed expert testimony amounts to good science, we may not ignore the fact that a scientist's normal workplace is the lab or the field, not the courtroom or the lawyer's office.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1317 (9th Cir. 1995). Expert testimony prepared solely for purposes of litigation, as opposed to testimony flowing naturally from an expert's scientific research or technical work should be viewed with some caution. *Magistrini*, 180 F. Supp. 2d at 594 (D.N.J.2002).

1. Dr. Bottorff's Methodology Was Fatally Flawed

"Both an expert's methodology and the application of that methodology must be reviewed for reliability." *In Re: Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d 787, 792 (3rd Cir. 2017), emphasis added. In *Player v. Motiva Enterprises LLC*, this Court

determined that an expert who failed to consider important facts without satisfactory explanation, among other things, failed the reliability requirement. *Player,* 2006 WL 166452, at *7 (D.N.J. January 20, 2006). This Court held: "His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any real standards." *Id.* at *8.

In this case, Dr. Bottorff's openly biased methodology was much worse than arbitrary, he intentionally only sought out literature that could provide some support for the opinions he was hired to give, as evidenced by his repeated admissions that he only looked for studies that showed low doses of NDMA not causing cancer, not doses that did. (Bottorff Dep. 162:7-10, 297:18-20, 303:24-304:10). This fact alone renders Dr. Bottorff's methodology unreliable and is grounds to exclude him entirely. **"[I]f the relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not acknowledge or account for that evidence, the expert's opinion is unreliable**." *In re Zoloft Products Liability Litigation,* 176 F. Supp. 3d 449, 460-61 (E.D. Pa. 2016), citing *In re Rezulin Products Liability Litigation,* 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005), emphasis added

In addition, as set forth above in detail, there are numerous additional methodological flaws underlying Dr. Bottorff's opinions. First, Dr. Bottorff employed a methodology to extrapolate NDMA exposure from rats to humans that is counter to recommendations by the WHO and FDA, in that the WHO specifies that with NDMA, **s**caling for variations in the ratios of surface area to body weight between rodent species and humans was not considered appropriate for the measures of exposure response, and even if scaling was appropriate, the FDA recommends multiplying by 50, not by 70 like Dr. Bottorff did. (Bottorff Dep. 280:16-281:2, 308:24-312:16; Bottorff Report p. 31-33; Ex. B; Ex. D). Dr. Bottorff also relied on underpowered studies for the basis of his

opinions. (Bottorff Dep. 200:19-21, 339:10-21). Furthermore, Dr. Bottorff failed to consider entire categories of evidence, such as mechanistic, dietary, and occupational exposure studies, because he only sought out studies that supported the opinion he was hired to give. (Bottorff Dep. 162:7-10, 297:18-20, 303:24-304:10; Bottorff Report). Finally, Dr. Bottorff did not determine the first-pass metabolism or liver saturation level of NDMA in humans and did not consider literature that evidenced low doses of NDMA orally ingested by humans getting into the systemic bloodstream, yet offered opinions founded on assumptions as to these points. (Bottorff Dep. 357:20-360:7, 362:12-18, 257:12-258:22). Therefore, Dr. Bottorff should not be permitted to opine that the levels of NDMA in valsartan are unable to get past the liver and go systemic. (Bottorff Report p. 28).

CONCLUSION

The combination of so many methodological flaws is more than enough to preclude all of Dr. Bottorff's opinions. This is especially true because Dr. Bottorff's flawed methodology resulted in opinions that are contrary to an overwhelming scientific consensus that NDMA and NDEA are probable human carcinogens.

For the foregoing reasons, Dr. Bottorff should be precluded from offering his opinions related to general causation.

Dated: November 1, 2021

Respectfully,

By: s/ C. Brett Vaughn
C. Brett Vaughn RN, BSN, JD
Hollis Law Firm
8101 College Blvd, Suite 260
Overland Park, KS 66210
Ph: 913-385-5400
Fax: 913-385-5402
Brett@HollisLawFirm.com

MDL PEC
COUNSEL FOR THE PLAINTIFFS